UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/[illegible]820	8/98	WANG H	CIT98-01PA

HM12/0509

PATRICIA GRANAHAN
HAMILTON BROOK SMITH & REYNOLDS
TOW MILITIA DRIVE
LEXINGTON MA 02173-7499

EXAMINER	
ANDRES, J	
ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 05/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/085,820	WANG ET AL.	
	Examiner	Art Unit	
	Janet L Andres	1642	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *4,6, 11,13,15-40 and 44-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-10,and 41-43* is/are rejected.

7)☒ Claim(s) *12 and 14* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,10* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-21 and 41-43, in paper No. 8 and subsequent election of category C, angiogenic factors affecting artery-specific molecules, specifying claims 1-3, 5-10, and 41-43, in paper No. 11, is acknowledged. Claims 12 and 14 also read on the elected species and are examined; claim 6 does not read on the elected species and is not examined. Claims 4, 6, 11, 13, 15-40, and 44-66 are withdrawn from consideration.

Claim Objections

1. Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. After the election of species, claims 12 and 14 become identical. Cancellation of one claim is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 5, 7-10, 12, 14 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The factors to be considered

have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-3, 5, and 7 are drawn to methods enhancing the interaction of an artery-specific molecule with a vein-specific molecule. The specification describes an artery-specific molecule, ephrin B2, that interacts with a vein-specific molecule, eph B4, but no guidance is presented for the identification of factors enhancing the interaction. While blocking the interaction between two molecules, for example by an antibody or a competing peptide, is art standard, enhancement of an interaction is less predictable. More direction than is present in the instant specification is required so that one of skill in the art would know what the characteristics of such factors might be, and how they might be identified. Further, even were there characteristics of factors enhancing the interaction of ephrin B2 and ephB4 described, it would not be predictable that these characteristics would provide sufficient guidance to enable one of skill in the art to identify factors enhancing the interaction of any artery-specific molecule with any vein-specific molecule, should such molecules exist. In the absence of such guidance, given the unpredictability of identifying enhancing factors, it would require undue

have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-3, 5, and 7 are drawn to methods enhancing the interaction of an artery-specific molecule with a vein-specific molecule. The specification describes an artery-specific molecule, ephrin B2, that interacts with a vein-specific molecule, eph B4, but no guidance is presented for the identification of factors enhancing the interaction. While blocking the interaction between two molecules, for example by an antibody or a competing peptide, is art standard, enhancement of an interaction is less predictable. More direction than is present in the instant specification is required so that one of skill in the art would know what the characteristics of such factors might be, and how they might be identified. Further, even were there characteristics of factors enhancing the interaction of ephrin B2 and ephB4 described, it would not be predictable that these characteristics would provide sufficient guidance to enable one of skill in the art to identify factors enhancing the interaction of any artery-specific molecule with any vein-specific molecule, should such molecules exist. In the absence of such guidance, given the unpredictability of identifying enhancing factors, it would require undue

experimentation by one of skill in the art to make and use the invention as described in the instant claims.

Claims 8-10, 12 and 14 are drawn to methods for targeting a drug to arteries in a mammal by administering a component that binds to an artery-specific molecule. While the specification describes a molecule, ephrin-B2, that is present on the surface of arterial endothelial cells but not venous endothelial cells, this molecule is known to be present in other tissue types (Pasquale, Curr. Opin. Cell. Biol. Vol. 9, pages 608-615, 1997). It would therefore not be predictable that agents directed against ephrin-B2 would target specifically to arteries; other tissues would also be affected. No other artery-specific molecules are described in the instant specification, nor are the characteristics by which such molecules might be identified presented. One of skill in the art would require further guidance and objective evidence indicating that specificity could be achieved and how it could be achieved, in order to make and use the invention as described in the instant specification.

4. Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method affecting the interaction between ephrin-B2 and eph-B4 comprising administering the extracellular region of ephB4, does not reasonably provide enablement for any other method of enhancing angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 41-43 are drawn to methods for affecting angiogenesis by administering a polypeptide comprising the extracellular domain of a vein-specific factor to a mammal. The most narrow limitation, that of claim 43, contemplates the administration of a polypeptide comprising the extracellular region of ephB4 to stimulate angiogenesis. While it might be expected that the extracellular region of ephB4 would bind to ephrin B2 and stimulate tyrosine phosphorylation of ephrin B2 and signal transduction (Bruckner et al., Science, vol. 275, pages 1640-1643, 1997), it is by no means clear that polypeptides comprising this extracellular domain would have this function. There is no indication of what additions to the extracellular region of ephB4 would be tolerated and what additions would not be tolerated. The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of what alterations can be made is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of induction of signalling through ephrin B2 are lacking, it is unpredictable as to which amino acid substitutions, if any, meet the limitations of the claim. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable. Therefore, one of ordinary skill would require guidance,

such as information regarding the extent of any additions, their location, and the specific amino acids which would result in the preservation of the stated activity. Therefore it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Further, even if specific alterations to the extracellular region of ephB4 that maintained its function in stimulating signaling through ephrin B2 were identified, the specification would still not be enabling for the more broadly drawn claims 41 and 42. Claim 41 requires the existence of a vein-specific molecule that interacts with an artery-specific molecule. While artery-specific responses are known and differences in cell-surface receptors between arteries and veins have been suggested (Simonet et al., European J. Pharmacology, vol. 216, pages 135-137, 1992), there are no examples of artery and vein-specific molecules other than ephrin-B2 and eph-B4 described in the instant specification or in the available art of record. It is therefore not predictable that other such molecules even exist. Further, no guidance is given as to how such molecules might be identified and no guidance regarding common structural features definitive of artery-specific molecules other than ephrin B2/eph-B4 is presented. It would therefore require extensive and undue experimentation for one skilled in the art to identify artery- and vein-specific molecules outside the ephrin/eph system, and further identify the characteristics of a stimulatory polypeptide comprising the extracellular region of the vein-specific polypeptide, so that one of skill in the art could make and use the invention as described. Claim 42 contemplates the administration of an extracellular

domain of an eph receptor. While the specification is enabling for the invention with respect to ephrin-B2 and the extracellular region of eph-B4 as addressed above, it is not predictable that other members of this signalling system would show a similar specificity or function as described in the instant claims. Ephrins and their receptors are widely distributed and understood primarily in their role in neural development (Pasquale, Curr. Opin. Cell. Biol. Vol. 9, pages 608-615, 1997). Their function in arterial and venous determination is an emerging field of research and no other examples of signalling pairs are described either in the instant specification or the available art of record. Further, no guidance as to how other similarly distributed pairs might be identified is provided and no evidence of common structural features correlative with such pairs is presented. Since the instant example was identified by generating a transgenic mouse, it would not be predictable that similar pairs could be identified, nor could a similar approach be taken without undue experimentation by one skilled in the art. Therefore, the method of claim 42 could not be practiced by one skilled in the art. One skilled in the art would require further guidance, in the form of less technologically complex approaches with a more predictable outcome in order to use the invention as claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 5, and 7 are drawn to methods affecting the "interaction" of artery- and vein-specific factors. However, "interaction" is not defined in the specification. In the absence of an explicit definition, the parameters defining an "interaction" would not be evident to one of skill in the art. One of skill in the art would therefore not be able to identify factors affecting said interaction.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (703) 308-3995. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via internet email regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

YVONNE EYLER, PH.D
PRIMARY EXAMINER

Janet L. Andres, Ph.D.
May 4, 2000